CARDIOVASCULAR, PHARMACOLOGY and CHEMISTRY

#447R1
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THE COUNCIL FOR TOBACCO RESEARCH - U.S.A.
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633 THIRD AVENUE
NEW YORK, N. Y. 10017

COMMITTEE:
Dr. Bing, Chm.
Dr. Jacobson
Dr. Cattell

Renewal
Application For Research Grant

Date: February 4, 1966

1. Name of Investigator: ULRICH SCHAEPPI, M.D.

2. Title: Staff Scientist

3. Institution & Address: WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY
222 Maple Avenue
Shrewsbury, Massachusetts 01545

4. Project or Subject: (A) Non-ganglionic Parasympathomimetic Action of Nicotine upon the Iris Sphincter.
(B) Changes in the Level of Vigilance Elicited by Administration of Nicotine to the Lower Brain Stem.

5. Detailed Plan of Procedure (Use additional pages if more space is required)

Summary

(A) Non-ganglionic Parasympathomimetic Action of Nicotine upon the Iris Sphincter.

We have observed that nicotine produces contraction of isolated mamalian iris sphincters. This effect occurs by a direct action of nicotine upon postganglionic parasympathetic nerve endings and leads to the release of cholinergic transmitter (and the latter induces then sphincter contraction). This interpretation is supported by the following observations:

1) the nicotine induced sphincter contraction shows the characteristic of a mechanism which is mediated by release of cholinergic transmitter (Schaeppi and Koella, 1964; Schaeppi and Dodd, 1965);

2) isolated iris sphincters react to physiological and pharmacological procedures like ganglion-free preparations (Schaeppi, 1966);

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3) nicotine fails to produce contraction of chronically parasympathetically denervated irides (Schaeppi and Dodd, 1965; Schaeppi, 1966).

In future work we wish to extend our observations on postganglionic parasympathomimetic effects of nicotine upon irides which will be investigated in vivo.

The iris sphincter serves as a model to demonstrate that nicotine stimulates the peripheral parasympathetic neuron not only at ganglionic sites (Magnus, 1905) but also at postganglionic nerve endings. This new mechanism of action of nicotine will help to understand (a) the action of nicotine upon other peripheral parasympathetic neurons (for instance those innervating coronary arteries), and (b) it will help to understand the nicotine effect upon brain systems containing cholinergic neurons.

For further information see appendix A.

Summary

(B) Changes in the Level of Vigilance Elicited by Administration of Nicotine to the Lower Brain Stem.

We have recently observed that nicotine injected into the 4th ventricle of unanesthetized paralyzed cats which are kept under local anesthesia produces a marked change in the level of vigilance which consists of a phase of arousal followed by a phase of reduced vigilance.

In the future we wish to further investigate the effects of the localized administration of nicotine to the brain stem. In particular we wish to study the effects of the injection of nicotine

1) into the blood supply to the lower brain stem;

2) into the cisterna magna;

3) into the 3rd ventricle;

4) also, we wish to investigate the effects of nicotine administration to localized areas on the floor of the 4th ventricle.

Injection of very small doses of nicotine into the 4th ventricle elicits marked changes in the level of vigilance of unanesthetized paralyzed cats. To what extent these nicotine effects play a role upon the production of psychic changes occurring in response to systemic administration of nicotine or in response to nicotine uptake during tobacco smoking remains to be seen.

For further information see appendix B.

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6. Budget Plan:

| | | |
|---|---|---|
| a. | Salaries Schaeppi=50%; Dodd=100% | $12,040 |
| b. | Expendable Supplies | 3,000 |
| c. | Other Expenses | 500 |
| d. | Permanent Equipment ** (see below) | 3,530 |
| e. | Overhead (15% of a, b, c) | 2,330 |
| | Total | $21,400 |

7. Anticipated Duration of Work: Two years.

8. Facilities and Staff Available: I have two laboratories at my disposal. Furthermore, a complete set-up for the investigation of pupillary changes. It consists of 1 Grass 2-channel polygraph, 1 S-4 Grass stimulator, a Heath Kit Oscilloscope for monitoring electrical stimulation. Sundry equipment as balances, etc., are likewise at my disposal. To investigate central effects of nicotine an operation table with a stereotaxic instrument is also available. Miss M. Dodd is full time technical assistant.

9. Additional Requirements: The $3,530.00 listed for aquisition of permanent equipment will be spent to buy the equipment listed on the attached page.

10. Additional Information (Including relation of work to other projects and other sources of support): 50% of my time will be used to investigate central mechanisms which are involved with the control of the cat's level of vigilance. This work is supported by a National Institute of Health grant to Dr. W. P. Koella.

** Permanent Equipment: (Grass Polygraph with accessories for recording of EEG, blood pressure, tension of nictitating membrane, etc.)

| | | |
|---|---|---|
| 6 channel console | | $ 550.00 |
| 4 driver amplifiers | 4 x $180.00 | 720.00 |
| oscillographs | 4 x 200.00 | 800.00 |
| signal marker | | 120.00 |
| preamplifiers - | | |
| low level DC 5P1 | 2 x 295.00 | 590.00 |
| low level AC | 3 x 125.00 | 375.00 |
| 1 Grass force displacement transducer | FT 03 | 125.00 |
| 1 Statham blood pressure strain gauge | P 23 AC | 250.00 |
| | | $3,530.00 |

Signature: Ulrich Schaeppi

Director of Project Ulrich Schaeppi, M. D.

Hudson Hoagland

Business Officer of the Institution Executive Director

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R: REDACTED MATERIAL

CURRICULUM VITAE

Ulrich H. Schaeppi, M. D.

REDACTED

CITIZENSHIP: American citizen

REDACTED CHILDREN: Four

EDUCATION: University of Zurich and Berne - M. D., 1951

EXPERIENCE: Resident in internal medicine, Kantonsspital Aarau, 1952-1955. Director: Professor Dr. A. Alder.
Resident-Institute of Pharmacology, University of Zurich, 1956-1957. Director: Professor Dr. P. Waser.
Pharmacologist, J. R. Geigy, A. G. Basel, 1957-1960. Director: Professor Dr. H. Wirz.
Neuropharmacologist, The Worcester Foundation for Experimental Biology, Shrewsbury, Mass., 1960 -
Director: Dr. W. P. Koella.

MILITARY SERVICE: Swiss Army (Rank: First Lieutenant).

PUBLICATIONS: Approximately 25 papers in scientific journals.

REDACTED

SPEAKING ENGAGEMENTS: Invited speaker at the international meeting sponsored by the New York Academy of Sciences April 7-9, 1966 in New York, N. Y. "The effects of nicotine and smoking on the central nervous system."

FINANCIAL SUPPORT: My work is supported in part by a personal research grant from The Council for Tobacco Research, U.S.A., and in part by a research grant from the National Institute of Health to Dr. W. P. Koella.

January, 1966

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(A) Non-ganglionic Parasympathomimetic Action of Nicotine upon the Iris Sphincter.

Present status of work:

The question whether nicotine stimulates autonomic effectors which are innervated by parasympathetic nerve fibers by an action upon ganglion cells only or whether it elicits also effects at postganglionic sites was not well understood in the past.

We have recently observed that nicotine produces contraction of the isolated iris sphincter of the pig (Schaeppi and Koella, 1964a). A grant from the Tobacco Research Council of U.S.A. for 1965-66 made it possible to further investigate this nicotine effect. In particular we were able to demonstrate that the pig iris reacts as if its parasympathetic nerve supply does not contain ganglion cells. This conclusion is borne out by observations that iris sphincters from eyes which were subjected to ciliary ganglionectomy two weeks prior to the in vitro investigation show the characteristic symptoms of chronic parasympathetic denervation. These symptoms consist of supersensitivity to small doses of acetylcholine and of neural inexcitability (Schaeppi, 1966). The observation that the parasympathetic nerve supply reacts as if it does not contain ganglion cells indicates then that the nicotine induced contraction of the isolated pig iris sphincter has to be attributed to a non-ganglionic site of action of nicotine. The further observation that nicotine fails to produce contraction of chronically parasympathetically denervated iris sphincters indicates that nicotine does not elicit contraction by a direct action upon the muscle fiber. It rather indicates that the nicotine induced contraction of the normal iris sphincter is due to the release of cholinergic transmitter from nerve endings or from structures depending upon an intact parasympathetic nerve supply. A detailed report on the postganglionic stimulating and blocking effects which nicotine exerts upon parasympathetic nerve endings in the pig iris sphincter has been published (Schaeppi and Dodd, 1965; Schaeppi, 1966), see also Figure A-1. The observation that nicotine produces postganglionic effects resembling those of peripheral parasympathetic stimulation can be compared with observations by Burn et al. (1959) who found that nicotine produces postganglionic effects resembling those of peripheral sympathetic stimulation.

Non-ganglionic effects of nicotine, similar to those observed in the isolated pig iris sphincter, can be found in isolated intact cat irides. A report on these observations is at present prepared for publication (Schaeppi and Koella, 1966) (see also Figure A-2).

Future work:

We wish to continue our work and to extend our observations on nicotine effects upon irides in vivo. Atkinson et al. (1965) recently have studied the effects of the intracarotid injection of nicotine in anesthetized cats. They observed that nicotine produced marked sympathomimetic effects but they failed to observe a postganglionic parasympathomimetic action. It must be expected that catecholamines which are released from the walls of the blood vessels to the iris may have contributed

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to the sympathomimetic action of nicotine and that strong sympathomimetic effects may then completely have masked parasympathomimetic effects of this compound.

In our future work we will investigate the effects of nicotine upon in vivo irides and we will inject nicotine into the anterior eye chamber of three different cat preparations.

Detailed plan of procedure:

Cats are operated under ether anesthesia. The trachea is cannulated and a polyethylene cannula is tied into the femoral vein. The size of both pupils is continuously monitored by means of a set of two pupillometers which are at present developed in our laboratories. Nicotine is injected locally into the anterior eye chamber by means of the following technique. A 22 gauge needle is inserted from the limbus corneae in a sense that the tip of the needle is located in the anterior eye chamber, in the center of the pupil. Thereafter, the needle is rigidly fastened and serves as a guide for a 28 gauge needle containing nicotine solution. Nicotine is dissolved in Tyrode solution and it is injected in 0.025 ml volumes. To maintain constant pressure within the eye ball a third needle is inserted into the anterior eye chamber and connected to a Tyrode reservoir with constant pressure. The nicotine effect is investigated in three different cat preparations:

1) Cats in deep Nembutal anesthesia in which the oculomotor nerve was transected within the skull are used to study the action of nicotine upon the mydriatic pupil. This preparation serves thus to demonstrate the miotic effects of nicotine.

2) Cats subjected to postcollicular pretrigeminal decerebration will be used as an in vivo preparation with firmly closed pupil. This preparation serves to demonstrate mydriatic effects of nicotine.

3) Cats maintained under deep pentobarbital anesthesia will be used to investigate the action of nicotine upon irides with intermediate pupillary size. These preparations will be used to investigate the biphasic response of nicotine which consists in miosis followed by mydriasis.

We will use only observations from cats in which nicotine failed to change the pupillary size of the non-treated control eye.

We also wish to investigate whether nicotine-induced miosis is mediated by a cholinergic mechanism. We will therefore investigate the effects of nicotine upon irides treated with atropine or inhibitors of cholinesterase and upon irides which were subjected to chronic parasympathetic denervation.

Significance:

Nicotine was found to produce stimulation of postganglionic parasympathetic nerve endings. This observation adds a new perspective to the mode of action of nicotine upon the cholinergic neuron, and contributes to a better understanding of the complex action of this compound. Whether this action has any bearing on experiments involving systemic administration of nicotine and particularly on long-term effects of smoking, remains to be seen.

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References to A:

Atkinson, R.A., Witt, D. and Long, J.P.,
Mechanisms of the sympathomimetic response of the cat iris to nicotine.
J. Pharmacol. expti. Therap. 157: 172-180, 1965.

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Peripheral effects of nicotine and acetylcholine resembling those of sympathetic stimulation.
J. Physiol. (London). 148: 332-352, 1959.

Magnus, R.,
Wirkundsweise und Angriffspunkte einiger Gifte am Katzendarm.
Arch. Ges. Physiol. 108: 1-71, 1905.

Schaeppi, U., and Koella, W.P.,
Reaction of isolated pig iris sphincter to electrical stimulation and acetylcholine.
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Schaeppi, U. and Dodd, M.,
Non-ganglionic effects of nicotine in the pig iris sphincter.
Life Science. 4: 1157-1160, 1965.

Schaeppi, U.,
Postganglionic nature of parasympathetic innervation of pig iris sphincter.
Am. J. Physiol. 210: 91-94, 1966.

Schaeppi, U., Rubin, R., and Koella, W.P.,
Electrical stimulation of the isolated cat iris.
Am. J. Physiol. (In Press).

Schaeppi, U., Dennison, B.L., and Dodd, M.,
Non-ganglionic parasympathomimetic action of nicotine upon the isolated cat iris.
(In Preparation for Publication).

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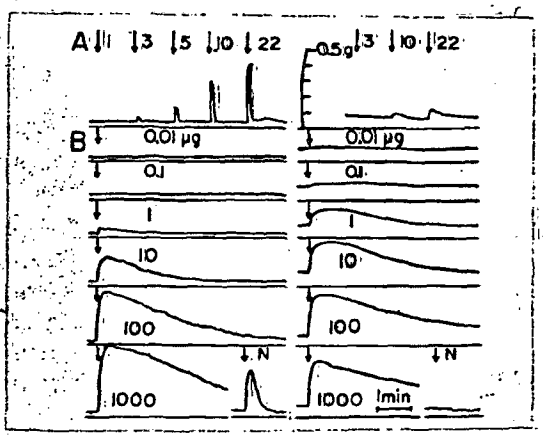
Appendix

Figure A-1: Tension changes of normal pig iris sphincter (column at left) and of contralateral chronically parasympathetically denervated iris sphincter (column at right) in response to electrical stimulation, acetylcholine and nicotine (N).




A: arrows indicate beginning of 5-sec periods of electrical stimulation with pulses of 1 msec duration at 15 pulses/sec and volts as indicated. B: arrows indicate administration of acetylcholine in doses as indicated except arrow marked N, which shows administration of 50 mg nicotine. Both preparations investigated at interhook distance of 9 mm. Both preparations same force calibration (grams). Note: Nicotine produces contraction of the normal sphincter but fails to produce contraction of the chronically parasympathetically denervated preparation.

From: Schaeppi, U., Am. J. Physiol. 210: 91-94, 1966.

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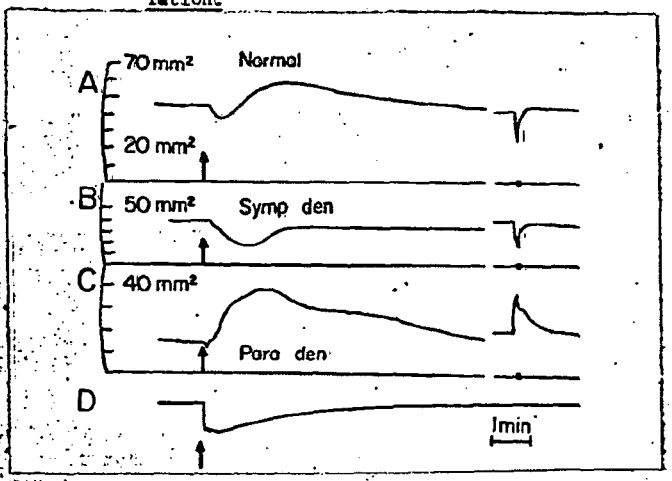
Figure A-2: Changes in pupillary size of isolated intact cat irides in response to administration of nicotine and in response to electrical stimulation.




Ordinate: pupillary size in $mm^2$. Abszissa: time. Arrows: A, B, and C injection of nicotine 10 mg. Markers: electrical stimulation with 5 sec trains of pulses of 2 msec pulse width, 3 pps at 20 volts. A: normal, B: chronically sympathetically denervated and C: chronically parasympathetically denervated intact cat iris. D: changes in transparency (arbitrary units) after a single injection of india ink. Iris replaced by metal plate with circular opening of 50 $mm^2$. Arrow injection of india ink. Flow rate of Tyrode 20 ml/min. Note: In normal irides nicotine produces closure followed by opening. After elimination of the parasympathetic nerve supply to the iris (chronically parasympathetically denervated iris) nicotine produces only opening. In the chronically sympathetically denervated iris nicotine produces only miosis.

From: Schaeppi, U., Dennison, B.L., and Dodd, M., "Non-ganglionic parasympathomimetic action of nicotine upon the isolated cat iris". (In Preparation for Publication)

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Source: https://www.industrydocuments.ucsf.edu/docs/jnwm0000

(B) Changes in the Level of Vigilance Elicited by Administration of Nicotine to the Lower Brain Stem.

Introduction:

Several investigators have demonstrated that electrical or chemical stimulation of the cat's lower brain stem exerts a marked effect upon the animal's level of vigilance. In encéphale isolé cats, electrical stimulation of the medulla elicits, in dependence upon the stimulus parameter and upon the site of stimulation, either symptoms of arousal or symptoms associated with a decrease in the level of vigilance (Magnes et al., 1961). The elimination of the lower brain stem by surgical procedures (Batini et al., 1959), or the inhibition by local treatment with anesthetics (Magni et al., 1959; Bonvallet and Bloch, 1961) induces a shift towards arousal. This arousal effect is due to the inactivation of medullary centers which exert a depressor effect upon more rostrally located brain structures. Strychnine injected into the cat's fourth ventricle produces generalized arousal (Schaeppi and Koella, 1966) and this effect must be attributed to the activation of excitatory structures which are located in the lower brain stem. Serotonin injected into the cat's fourth ventricle induces a protracted decrease in the cat's level of vigilance and this effect was found to be due to the activation of chemoreceptors in the area postrema which induces the activation of medullary depressor centers (Koella et al., 1965).

Nicotine was repeatedly shown to have a direct action upon the lower brain stem of the cat. Medullary actions of nicotine consist in emesis (Laffan and Borison, 1957) and in changes in the rate and in the amplitude of respiration (Nicholson and Sobin, 1938; Mitchell et al., 1963). It was therefore of interest to investigate medullary effects of nicotine upon the cat's level of vigilance.

Present status of work:

Fifteen cats, paralyzed with Flaxedil, were artificially respirated and kept under local anesthesia. The level of vigilance was determined by recording cortical EEG, tension of the nictitating membrane, size of pupil, blood pressure and ECG. Nicotine HCl was dissolved in Tyrode, neutralized, and injected in volumes of 0.025 ml into the fourth ventricle. Nicotine produced arousal in drowsy and sleeping cats. The arousal often was interrupted by short periods of EEG synchronization with decreased sympathetic activity. The phase of arousal usually was followed by a phase of reduced level of vigilance. The threshold dose for these nicotine effects was about 1 µg. (see Figure B-1.) (Schaeppi, U., 1966.)

Future work:

Nicotine administered to the medulla of cats affects respiration in a dual way and this dual action has been shown to be caused by an action upon at least two different medullary sites (Mitchell et al., 1963). It is therefore very likely that the dual nicotine effect upon the cat's level of vigilance is also due to a multiple site of

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action upon the medulla. To further localize these sites we wish to continue our work with Flaxedil paralyzed cats and we wish:

1) to further investigate the action of nicotine injected into the cat's fourth ventricle;

2-3) to investigate the effects of nicotine injected into the cisterna magna and into the third ventricle;

4) to investigate the action of nicotine injected into the blood supply to the lower brain stem;

5) to investigate in cerebellectomized cats the effects of the local application of nicotine to various areas on the floor of the fourth ventricle;

6) to investigate the effects of nicotine administration into the fourth ventricle of unrestrained, free moving cats.

Detailed plan of procedure:

1) preparation and recording techniques:

Cats are tracheotomized under ether anesthesia and a polyvinyl cannula is tied into the femoral vein. The head is placed in a stereotaxic instrument and burr holes are drilled into the exposed skull (11 mm laterally from the sagittal suture and 12, 15 and 18 mm posterior from the coronal suture). Silver electrodes mounted on a lucite holder are inserted in the burr holes in a sense that the uninsulated tip is located on the dura. The lucite holder is fastened with screws to the skull. After termination of the surgical procedure the wound margins are infiltrated with 1% Xylocaine solution, the cats are maintained under artificial respiration and kept paralyzed with i.v. injection of Flaxedil 1 ml/hour. The electrocorticogram from the suprasylvian gyrus is recorded against an indifferent screw electrode on the frontal bone. The EEG from the medulla is monitored by means of stainless steel electrodes (Hess) which are mounted on a microdrive, and which are vertically inserted into the medulla. The EEG from the medulla is recorded from the area of the solitary nucleus against an indifferent screw electrode on the frontal bone. For electrical recording two 4 channel Grass polygraphs are used. The cortical EEG is routinely fed into an EEG Offner frequency analyzer whose output is recorded at 10 sec delay on the polygraph. The following indicators are also recorded on the polygraph: the blood pressure from the femoral artery by means of a Statham strain gauge, the tension of the nictitating membrane by means of a Grass force transducer and the size of the pupil by means of a pupillometer which was recently developed in our laboratories (Dennison, to be published).

2) a) For cannulation of the 4th ventricle a 22 gauge needle with short bevel is mounted on a microdrive. The cannula enters the skull through a burr hole in the crista occipitalis 3 mm in front of the eminentia occipitalis. The cannula is directed

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in the sagittal plane at an angle of from 60 to 70 degrees with the horizontal plane, and it is inserted until the tip reaches the fourth ventricle.

b) For cannulation of the cisterna magna the 22 gauge cannula is inserted horizontally through the membrana atlanto occipitalis. The needle perforates the membrane at the dorsal edge of the foramen magnum.

c) For cannulation of the third ventricle a 22 gauge cannula is inserted vertically through the parietal bone. It is oriented in the sagittal plane, enters the parietal bone through a burr hole in the sagittal suture, 12.5 mm anterior to the interauricular line, and it is inserted until it reaches the 3rd ventricle. To prevent nicotine injected into the 3rd ventricle from reaching pontine and medullary structures the liquor outflow from the 3rd ventricle is collected by means of a polyethylene tube which is inserted in the aqueduct of the midbrain. For insertion of this tube the cat is cerebellectomized and the tube is inserted under visual control.

d) To inject nicotine into the 4th ventricle of unanesthetized unrestrained cats we will use the technique of ventricular cannulation as reported by Feldberg and Sherwood (1953). We will use principally the same transcerebellar approach as described in (a) above.

e) For the application of nicotine to localized areas on the floor of the 4th ventricle the cerebellum is removed under local anesthesia. Cotton pellets of 2 mm diameter soaked with nicotine dissolved in Tyrode solution are applied to various areas on the floor of the 4th ventricle.

f) Nicotine is administered into the blood supply to the lower brain by injecting it into the vertebral artery according to the technique introduced by Magni et al. (1959). Cats are tracheotomized under ether anesthesia and are subjected to section of the spinal cord at C2 and to bilateral cervical vagotomy. The palate vault is trephined, the basilar artery exposed and ligated at a caudal pontine level slightly anterior to the foramen caecum. The right vertebral artery is exposed and cannulated. According to observations by Magni et al. (1959) material injected into the right vertebral artery is conveyed to the medulla, and to the caudal portion of the pons, up to the trapezoid body. The distribution is prevalently, but by no means exclusively, ipsilateral.

For intraventricular administration nicotine HCl is dissolved in Tyrode solution, adjusted to a pH of 7-7.2, kept at from 37.5 to 39 centigrades and is injected in 0.025 ml volumes through a 28 gauge needle which is inserted into the lumen of the 22 gauge cannula. Nicotine injections are repeated at intervals of approximately 1 hour. Between each subsequent nicotine injection 0.025 ml Tyrode is injected as control. Injections are performed within a 30 sec period. The volumes of the injected solutions are well within the order of magnitude of the volumes of cerebrospinal fluid secreted into the cerebral ventricles (0.02 ml/min according to Davson et al., 1962).

Significance:

Injection of very small doses of nicotine into the 4th ventricle elicits marked changes in the level of vigilance of unanesthetized paralyzed cats. To what extent these nicotine effects play a role upon the production of psychic changes occurring in response to systemic administration of nicotine or in response to nicotine uptake during tobacco smoking remains to be seen.

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References to B:

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EEG Arousal Following Inactivation of the Lower Brain Stem by Selective Injection of Barbiturate into the Vertebral Circulation.
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Respiratory effects from the application of cocaine, nicotine and lobeline to the floor of the fourth ventricle.
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Schaeppi, U., and Koella, W.P.,
Changes in level of vigilance in response to administration of drugs into the 4th ventricle of the cat.
Fed. Proc., 1966 (In Press).

References to B -

Schaeppi, U.,
Effect on level of vigilance of nicotine injected into the cat's 4th ventricle or cisterna magna.
To be reported at the meeting of the New York Academy of Sciences, New York. April 6-7, 1966.

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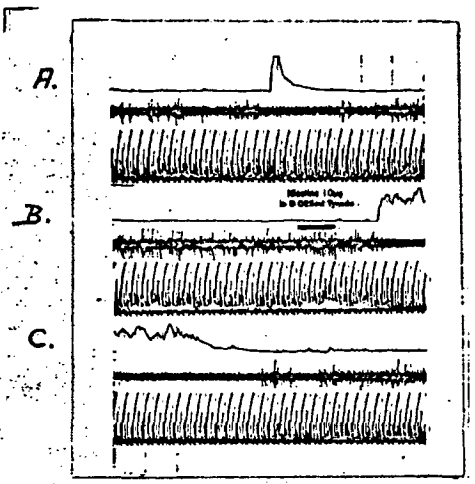
Figure B-1: Changes in level of vigilance in response to injection of nicotine (10 γg) into the 4th ventricle of unanesthetized, paralyzed cat.




Records A, B, C. Top line: tension of nictitating membrane. Second line: EEG, monopolar recording from middle suprasylvian gyrus against screw electrode on frontal bone. Third line: frequency analysis of EEG (10 sec delay). A: control, B: marker indicates 30 sec period of nicotine injection, C: return to control level.

Note: Nicotine injection into the 4th ventricle of the cat produces contraction of nictitating membrane and EEG desynchronization. These symptoms of arousal lasted approximately 4 minutes.

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Source: https://www.industrydocuments.ucsf.edu/docs/jnwm0000

PUBLISHED PAPERS

Ulrich H. Schaeppi, M. D.

1953 - 1963

1. Dissertation. On the cancerogenic effect of methyl violet (Methylrosaniline Chloride). U. Schaeppi. Dis. University of Berne, 1953.

2. Cholinolytische Wirkung einiger Phenothiazin-, Xanthen- und Anilin-Koerper und ihre Beziehung zur chemischen Struktur. (Cholinolytic effect of some Phenothiazine-, Xanthen- and Anilin- derivatives in relation to their chemical configuration). U. Schaeppi and P. Waser. Arzneim.-Forsch. 8: 107-113, 1958.

3. Die Beeinflussung der Reizuebertragung imperipheren Sympathicus durch Tofranil. (Interaction of Tofranil with the impulse transmission in the peripheral sympathetic system.) U. Schaeppi. Helv. Physiol. Acta. 18: 545-552, 1960.

4. Effects of pentothal on neural activity in somatosensory cortex and brain stem in cat. S. Yamamoto and U. Schaeppi. Electroenceph. clin. Neurophysiol. 13: 248-256, 1961.

5. The reaction of the isolated cat iris to serotonin. W. P. Koella and U. Schaeppi with technical assistance of S. Gustafson and A. Bloch. J. Pharmacol. Exptl. Therap. 138: 154-158, 1962.

6. Effect of neurohumors on the nictitating membrane of the cat. U. Schaeppi. Fed. Proc. 21: 330, 1962.

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